REMARKS

I. Rejection under 35 USC 103(a) in view of De Bono et al. and Lokich et al.

Claims 47 and 58 are rejected as being obvious in view of the abstract by De Bono et al. in combination with the article by Lokich et al. This rejection is respectfully traversed.

The abstract by De Bono et al. (2002) discloses the results of an assessment study on the administration of troxacitabine. In the study, troxacitabine was administered "as a 30-minute intravenous (IV) infusion daily for 5 days." Thirty-nine patients were given "124 courses troxacitabine at eight dosage levels ranging from 0.12 to 1.8 mg/ml/d." At dosage levels of 1.2 mg/ml/d, the treatment interval was lengthened "from every 3 to 4 weeks." The study concluded that a dosage regime of "30-minute infusion for 5 days every 4 weeks" was recommended for phase II studies.

As noted in the rejection, abstract by De Bono et al. does not disclose administering an amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours. In fact, the recommendation of the study suggests a very different dosage regime, i.e., a 30-minute infusion for 5 days every 4 weeks. Clearly, the abstract by De Bono et al., particularly in light of the dosage regime recommended for phase II studies, does not provide any rationale that would lead one of ordinary skill in the art to select an administration regime in which a patient was administered troxacitabine by continuous infusion for a period of at least 72 hours.

Lokich et al. (1997), which was published before the De Bono et al. abstract, describe the results of a literature survey analyzing the relative dose intensity (DI) and maximum tolerated dose (MTD) for bolus versus infusional administration techniques for 27 anti-neoplastic agents. It is noted that troxacitabine is **not** one of the 27 anti-neoplastic agents included in the analysis.

The rejection argues that Lokich et al. disclose that some anti-neoplastic agents, such as 5-fluoruracil and cladrabine, are administered as a continuous 24-hour infusion for five or more days, and that the rationale for administration by infusion is "based upon observing schedule dependency in experimental systems and drug pharmacology in which a short plasma half-life following bolus administration would limit tumor cell exposure." See page

15. Additionally, Lokich et al. disclose at the bottom of page 15:

> Infusional schedules employ various durations of administration including 24-hour infusion repeated at weekly or longer intervals; 96-120-hour infusions; 7- or 14-day infusions; and finally the protracted infusion for weeks or months. The selection of a duration of infusion is often arbitrary or based on achieving specific objectives such as decreasing allergic, gastrointestinal or other adverse effects.

In the rejection, it is asserted that it would be obvious to manipulate the continuous infusion of troxacitabine taught by De Bono et al. in light of the disclosure of Lokich et al. so as to arrive at an embodiment in accordance with applicants' claimed invention. Applicants respectfully disagree.

The disclosure of Lokich et al. does not include troxacitabine in its analysis of 27 anti-neoplastic agents. Thus, only the abstract by De Bono et al. deals directly with the administration of troxacitabine, and specifically administration of troxacitabine by infusion. The conclusion of De Bono et al. is to use a very different dosage regime for infusional administration of troxacitabine than that involved in applicants' claimed invention.

The assertion that it would be obvious to optimize based on the Lokich et al. disclosure does not suggest modifying the procedure of De Bono et al. The study of De Bono et al., which is subsequent to the Lokich et al. disclosure, seeks to optimize the infusion of troxacitabine and the result is a suggested dosage regime that clearly differs from that claimed by applicants. One of ordinary skill in the art presented with the disclosures of De Bono et al. and Lokich et al. would not modify De Bono et al.'s infusional dosage regime specific for troxacitabine based on a literature survey that did not include results for troxacitabine.

Alternatively or additionally, one of ordinary skill in the art may not have any expectation as to the optimal methodology for administering troxacitabine based on the disclosure of Lokich et al. Unlike Ara-C and other nucleoside analogues used as anti-neoplastic agents, troxacitabine was the first unnatural L-nucleoside analog to show potent preclinical anti-tumor activity, thus effecting representing a new class of agents. Overall, the disclosure of Lokich et al. does not suggest the particular administration regime for troxacitabine recited in applicants' claims.

In view of the above remarks, it is respectfully submitted that the disclosure of De Bono et al., taken alone or in combination with the disclosures of Lokich et al., fails to render

obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

II. Rejection under 35 USC 103(a) in view of De Bono et al., Lokich et al., and Chu et al.

Claims 1, 3-15, and 17-38, 48-56, and 58-60 are rejected as being obvious in view of the abstract by De Bono et al., the article by Lokich et al., and Chu et al. (US 5,817,667). This rejection is respectfully traversed.

The abstract by De Bono et al. and the article by Lokich et al. are discussed above. With regards to Chu et al. (US '667), it is argued in the rejection that this patent discloses using troxacitabine in the treatment of cancers. At column 3, lines 49-52, Chu et al. specifically mention, for example, lung, colorectal, breast, prostate, bladder, pancreatic, ovarian, leukemia, and lymphoma cancers.

At column 11, lines 8-12, Chu et al. disclose that troxacitabine is "preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30 mM, preferably about 0.1-30 μM." Additionally, at column 10, lines 55-59, Chu et al. disclose that troxacitabine can be administered "either alone, or in combination with other known anticancer or pharmaceutical agents" and can be combined "with other conventional cancer therapies, such as radiation treatment or surgery."

However, Chu et al. do not disclose administering troxacitabine or a pharmaceutically acceptable salt thereof by infusion, let alone continuous infusion, let alone continuous infusion for a period of at least 72 hours. Thus, as with the disclosure of Lokich et al., the Chu et al. disclosure provides no rationale for modifying the dosage regime disclosed by De Bono et al. in such a manner as to arrive at an embodiment in accordance with applicants' claimed invention.

In view of the above remarks, it is respectfully submitted that the disclosure of De Bono et al., taken alone or in combination with the disclosures of Lokich et al. and/or Chu et al., fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

III. Rejection under 35 USC 103(a) in view of De Bono et al., Lokich et al., Chu et al., and Boote et al.

Claim 39 is rejected as being obvious in view of the abstract by De Bono et al., the article by Lokich et al., Chu et al. (US 5,817,667), and the article by Boote et al.. This rejection is respectfully traversed.

The abstract by De Bono et al., the article by Lokich et al., and the disclosure of Chu et al. (US 667) are discussed above. With regards to the article by Boote et al., this article describes the results of a study to determine the maximum-tolerated dose and toxicity of PSC 833 infusion when administered in combination with etoposide. In the study, PSC 833 was administered as a 2-hour loading dose and as a 5-day continuous infusion. Etoposide was administered as a 2-hour infusion over 5-days.

However, Boote et al. do not disclose or suggest administering troxacitabine or a pharmaceutically acceptable salt thereof by infusion, let alone continuous infusion, let alone continuous infusion for a period of at least 72 hours. Thus, as with the disclosures of Lokich et al. and Chu et al., the Boote et al. disclosure provides no rationale for modifying the dosage regime disclosed by De Bono et al. in such a manner as to arrive at an embodiment in accordance with applicants' claimed invention.

In view of the above remarks, it is respectfully submitted that the disclosure of De Bono et al., taken alone or in combination with the disclosures of Lokich et al., Chu et al., and/or Boote et al., fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

IV. Rejection under 35 USC 103(a) in view of De Bono et al., Lokich et al., Chu et al., and Goodman & Gilman's

Claims 40-42 are rejected as being obvious in view of the abstract by De Bono et al., the article by Lokich et al., Chu et al. (US 5,817,667), and the excerpt from Goodman & Gilman's. This rejection is respectfully traversed.

The abstract by De Bono et al., the article by Lokich et al., and the disclosure of Chu et al. (US 667) are discussed above. With regards to the excerpt from Goodman & Gilman's, the rejection argues that this disclosure describes the biologic response modifier α-interferon and its use in the treatment of melanoma. See the top of the Table on page 1229.

However, the excerpt from Goodman & Gilman's does not disclose or suggest administering troxacitabine or a pharmaceutically acceptable salt thereof by infusion, let alone continuous infusion, let alone continuous infusion for a period of at least 72 hours. Thus, as with the disclosures of Lokich et al. and Chu et al., the excerpt from Goodman & Gilman's provides no rationale for modifying the dosage regime disclosed by De Bono et al. in such a manner as to arrive at an embodiment in accordance with applicants' claimed invention.

In view of the above remarks, it is respectfully submitted that the disclosure of De Bono et al., taken alone or in combination with the disclosures of Lokich et al., Chu et al., and/or Goodman & Gilman's, fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

V. Rejection under 35 USC 103(a) in view of De Bono et al., Lokich et al., Chu et al., and Schwartz et al.

Claims 43-46 are rejected as being obvious in view of the abstract by De Bono et al., the article by Lokich et al., Chu et al. (US 5,817,667), and Schwartz et al. (US 6,444,638). This rejection is respectfully traversed.

The abstract by De Bono et al., the article by Lokich et al., and the disclosure of Chu et al. (US 667) are discussed above. Schwartz et al. disclose a method of treating cancer which comprises administering at least one antitumor therapeutic agent such as paclitaxel, and at least one modulating agent such as flavopiridol, either sequentially or concomitantly. See column 6, lines 53-62.

However, Schwartz et al. do not disclose or suggest administering troxacitabine or a pharmaceutically acceptable salt thereof by infusion, let alone continuous infusion, let alone continuous infusion for a period of at least 72 hours. Thus, as with the disclosures of Lokich et al. and Chu et al., the disclosure of Schwartz et al. provides no rationale for modifying the dosage regime disclosed by De Bono et al. in such a manner as to arrive at an embodiment in accordance with applicants' claimed invention.

In view of the above remarks, it is respectfully submitted that the disclosure of De Bono et al., taken alone or in combination with the disclosures of Lokich et al., Chu et al., and/or Schwartz et al., fails to render obvious applicants' claimed invention. Withdrawal of

the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Brion P. Heaney/

Brion P. Heaney, Reg. No. 32,542
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza 1
2200 Clarendon Boulevard, Suite 1400
Arlington, VA 22201
Direct Dial: 703-243-6333
Facsimile: 703-243-6410
Attorney Docket No.: STROMIX-8

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